Bictegravir use during pregnancy: a multi-center retrospective analysis evaluating HIV viral suppression and perinatal outcomes

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This study describes the largest cohort to date (n=147) of pregnant patients living with HIV on bictegravir (BIC). BIC in pregnancy was associated with high levels of viral suppression and...
similar perinatal outcomes to published literature. These findings support consideration for use of BIC in management of HIV during pregnancy.

Key Words: Pregnancy, HIV, Biktarvy, Perinatal Outcomes

INTRODUCTION/BACKGROUND:

Approximately 1.3 million females living with HIV worldwide become pregnant annually\(^1\). In non-breastfeeding people the transmission rate can be reduced to <1% with combination antiviral therapy (ARV)\(^2\). For people living with HIV who become pregnant, the current recommendations are to continue their ARVs \(^3\). Many people use new, first-line medications prior to pregnancy, and it is recommended to continue these ARVs during pregnancy; however pregnancy specific safety, efficacy, and perinatal outcome data significantly lag behind\(^3\). This often means, patients are taken off their prepregnancy ARVs.

Bictegravir (BIC) was approved in February 2018 and is available as a co-formulated single once daily tablet with emtricitabine and tenofovir alafenamide (Biktarvy). Given bictegravir is only available in this coformulation, this study looks at outcomes on bictegravir with emtricitabine and tenofovir alafenamide. Bictegravir has high efficacy, safety, tolerability, and genetic barrier to resistance \(^4,5\). Biktarvy is recommended as first-line therapy for use in treatment-naïve patients and those with viral suppression. As of January 2024, bictegravir is an alternative ARV regimen in pregnancy per the HIV Perinatal Guidelines\(^3\). At the time of writing, there are two published case reports on BIC use in pregnancy, and one open label multicenter phase 1b study in 33 pregnant women\(^5,6\). While these found no safety concerns for either the infant or mother, BIC use in real world practice has not been investigated on a larger scale \(^5,6\).

Pharmacokinetic changes in pregnancy may lead to lower plasma levels of some ARV drugs and necessitate frequent viral load monitoring, or rarely a change in ARV regimen\(^3\). Additionally, there are special considerations for medication use in pregnancy regarding fetal safety and potential effects on perinatal outcomes. Given the limited clinical data available regarding the use of BIC during pregnancy, despite it being a first line HIV medication outside of pregnancy, this study aims to describe maternal viral suppression and perinatal outcomes in people using BIC during pregnancy.

METHODS:

This was a multicenter retrospective review of the clinical experience using BIC in pregnancy at four sites - Grady Health System (Atlanta, Georgia), University of Pennsylvania (Philadelphia, Pennsylvania), Baylor College of Medicine (Houston, Texas), and University of Miami (Miami, Florida). We included any pregnant patient who presented for care between Jan 1, 2019, and Jan 9, 2023, received BIC at any point during pregnancy, were (1) between the age of 12-50 years,
(2) living with HIV and (3) had available pregnancy outcome data. Those who delivered at outside hospitals, were lost to follow up prior to delivery, and/or did not have complete HIV medication history during pregnancy were excluded. Each site reviewed the medical records and entered deidentified data into a shared, password-protected database. The study was approved at each site’s Institutional Review Board.

Demographics, HIV, perinatal, and infant outcomes were abstracted, and outcomes analyzed according to timing of BIC use in pregnancy: 1) Preconception BIC with continued use in pregnancy, 2) Started BIC during pregnancy, 3) Preconception BIC but discontinued during pregnancy. Preconception BIC use was defined as being on BIC at initial prenatal visit and continued use through delivery. Participants were described as starting BIC use in pregnancy if they entered pregnancy not on medications or on a different regimen, and then started BIC in pregnancy. Viral suppression was defined as HIV-1 RNA (viral load) <50 copies/mL. Data was also collected on rate of viral load <200 copies/mL. The HIV outcomes included were viral load, CD4 count, route of transmission and rate of perinatal transmission. Perinatal outcomes included gestational age at delivery, birth weight, route of delivery, and birth anomalies.

RESULTS:

A total of 147 pregnancies with BIC use were included (Site 1 [n=41], Site 2 [n=18], Site 3 [n=75], Site 4 [n=13]). The mean age was 29 (range 16-43) years, and the mean gestational age of delivery was 39 (range 26-41) weeks. The average gestational age at entry to prenatal care was 17 weeks (range 6-35). Of the participants, 8.3% (12/145) acquired HIV perinatally. Of the included pregnancies, 83 (57%) received preconception BIC with continued use in pregnancy, 59 (40) started BIC during pregnancy, and 5 (3%) received preconception BIC but discontinued during pregnancy (Table 1).

With any BIC use during pregnancy, 90.3% were virally suppressed (HIV RNA <50) at the time of delivery: 96.2% in the group that received preconception BIC with continued use in pregnancy, 84.7% in those that started BIC during pregnancy, and 60% in those that were switched off BIC during pregnancy. In the group that started BIC during pregnancy, the average gestational age at initiation was 24.7 (range 6-34) weeks. Of those who started BIC during pregnancy, 91.5% achieved HIV viral load of <200 copies/mL by the time of delivery. With using a VL <50 copies/mL as definition of suppression, 9 out of the 59 that were started on BIC in pregnancy were detectable at the time of delivery. Of these 9 participants, 2 had <4 weeks on BIC and 7 had >4 weeks on BIC. Of the 2 detectable patients with < 4 weeks of BIC; 1 had documented compliance issues and the other only had 1 week of medication. Of the 7 with more than 4 weeks of BIC, compliance issues were noted in most, however this information was not universally collected in a consistent manner.
There were no cesarean deliveries for elevated HIV viral load in the group who received preconception BIC and continued use in pregnancy. There were 5 cesarean deliveries due to HIV in those who were started on BIC during pregnancy, and 1 who discontinued BIC in pregnancy. In those who discontinued BIC (n=5), three were switched due to side effects, and two for unknown reasons.

Overall, 17.7% experienced preterm birth (delivery at <37 weeks), including 19.2% (16/83) for those on preconception BIC with continued use in pregnancy, 16.9% (10/59) in those who started BIC during pregnancy, and 0% (0/5) for those on preconception BIC but discontinued during pregnancy. Of those in the study who experienced a preterm delivery, some had conditions that may have increased their preterm birth risk above baseline; including but not limited to hypertensive disorders (10/26), or multifetal gestation (3/26).

For those on preconception BIC with continued use in pregnancy, a congenital anomaly was noted in 2.4% - one infant with Tetralogy of Fallot and penis chordae, and one with mosaic 8p, an atrial septal defect, and agenesis of the corpus callosum. With regards to those who started on BIC during pregnancy and had a congenital anomaly, the average ARV start time was after the first trimester. (Table 1)

In all the pregnancies included, one perinatal HIV transmission occurred in a patient who entered prenatal care at 31 weeks with likely acute HIV infection during pregnancy. BIC was started at 31 weeks at which time the patient had a high viral load around 20,000 copies/mL. The infant had positive HIV RNA twice within 24 hours of birth, and thus the transmission was deemed an intrauterine infection.

DISCUSSION:

In this analysis, the use of BIC in pregnancy was associated with high levels of viral suppression and similar perinatal outcomes to published literature in this population. The group on preconception BIC with continued use in pregnancy had the highest frequency of viral suppression at delivery. Notably, this group also had improvement in viral suppression from entry to care to delivery (79.2% to 96.2%), likely related to medication adherence. This finding supports pharmacokinetic data that dose adjustment is not needed in pregnancy for BIC. The rate of viral suppression on BIC in our study is comparable to a recent study including the currently preferred regimen in pregnancy (dolutegravir-containing) with 93.1% viral suppression. The slightly lower rate of viral suppression (84.7%) in those who started BIC in pregnancy is likely related to confounding factors such as later initiation of prenatal care and not secondary to the medication efficacy.

The rate of preterm birth (PTB) in this study was 17.7% overall and 19.2% in the group that continued BIC throughout pregnancy. The rate of PTB in this cohort is elevated when compared...
to the national rate (10.4%)\textsuperscript{10}, however in Hispanic Black women, the PTB rate is about 50% higher than White women at 14.4% \textsuperscript{10}. Additionally, studies in pregnant persons with HIV have shown PTB rate 3-4 x higher than general population\textsuperscript{11}. More studies are needed to understand the impact of BIC, other ARVs, and HIV on the preterm birth rate in the context of other risk factors in this population.

The overall rate of fetal anomalies was 4.1% in this cohort and 2.4% in preconception BIC with continued use in pregnancy. This is comparable to the incidence of birth defects in the general population. The interactions between medication use in pregnancy and birth defects are complex and are specific to the dose, timing of exposure, duration, interaction with other exposures, and maternal/fetal genetics. In general, birth outcomes are needed from at least 200 infants exposed to a medication in the first trimester to detect a doubling of the risk of overall birth defects associated with that drug (assuming a general prevalence of 3%)\textsuperscript{3}. While the findings of this study are reassuring for the safety of BIC in pregnancy, it was not adequately powered to evaluate risk of birth defects.

The case of perinatal HIV transmission (deemed intrauterine infection) occurred in the setting of presumed acute HIV seroconversion in pregnancy which is associated with a significantly increased risk of perinatal HIV transmission\textsuperscript{12}. In this case, BIC was started at 31 weeks upon entry to prenatal care and was effective in achieving rapid viral suppression, as the viral load was undetectable by 34 weeks.

Limitations of this study include the retrospective design, limited sample size to detect difference in perinatal outcomes by timing of BIC, and data generated only from academic medical centers with infrastructure and experience in managing HIV in pregnancy. Despite these limitations, relative to the published literature, we present a large, “real world” cohort of pregnant patients receiving BIC from four diverse medical centers. Our results demonstrate high viral suppression and favorable safety profile of BIC used during pregnancy, supporting its use in the management of HIV during pregnancy.

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++ There are no conflicts of interest for all corresponding authors.

References:


\textsuperscript{2}AIDS 2014 Apr 24;28(7):1049-57. doi: 10.1097/QAD.0000000000000212.

\textsuperscript{3}Panel on Treatment of HIV During Pregnancy and Prevention of Perinatal Transmission. Recommendations for the Use of Antiretroviral Drugs During Pregnancy and Interventions to


DOI: 10.1093/cid/ciae218
Table 1: HIV viral suppression and perinatal outcomes with use of bictegravir (BIC) in pregnancy

<table>
<thead>
<tr>
<th></th>
<th>Preconception BIC with continued use in pregnancy (n=83)</th>
<th>Started BIC during pregnancy (n=59)</th>
<th>Preconception BIC but discontinued during pregnancy (n=5)</th>
<th>Any BIC use in pregnancy (n=147)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Background</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Mean age in years (range)</td>
<td>29.2 (19-43)</td>
<td>28.3 (16-42)</td>
<td>23.4 (19-28)</td>
<td>28.6 (16-43)</td>
</tr>
<tr>
<td>Non-Hispanic Black</td>
<td>62/83 (74.7%)</td>
<td>47/59 (79.7%)</td>
<td>2/5 (40%)</td>
<td>111/147 (75.5%)</td>
</tr>
<tr>
<td>White</td>
<td>1/83 (1.2%)</td>
<td>1/59 (1.6%)</td>
<td>0/5 (0%)</td>
<td>2/147 (1.4%)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>20/83 (24.1%)</td>
<td>10/59 (16.9%)</td>
<td>2/5 (40%)</td>
<td>32/147 (21.7%)</td>
</tr>
<tr>
<td>Identified as Other Race</td>
<td>0/83 (0%)</td>
<td>1/59 (1.6%)</td>
<td>1/5 (20%)</td>
<td>2/147 (1.4%)</td>
</tr>
<tr>
<td>Perinatal HIV infection</td>
<td>6/82 (7.3%)</td>
<td>5/58 (8.6%)</td>
<td>1/5 (20%)</td>
<td>12/145 (8.3%)</td>
</tr>
<tr>
<td>Sexual HIV infection</td>
<td>50/83 (60.2%)</td>
<td>47/59 (79.7%)</td>
<td>3/5 (60%)</td>
<td>100/147 (68%)</td>
</tr>
<tr>
<td><strong>HIV Outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV-1 RNA viral load &lt;50 copies/mL on entry to prenatal care</td>
<td>65/82 (79.2%)</td>
<td>13/56 (23.2%)</td>
<td>4/5 (80%)</td>
<td>82/143 (57.3%)</td>
</tr>
<tr>
<td>HIV-1 RNA viral load &lt;200 copies/mL on entry to prenatal care</td>
<td>70/82 (85.3%)</td>
<td>16/56 (28.6%)</td>
<td>5/5 (100%)</td>
<td>91/143 (63.6%)</td>
</tr>
<tr>
<td>CD4 &lt;200 cells/mm³ at prenatal care entry</td>
<td>4/82 (4.9%)</td>
<td>13/58 (22.4%)</td>
<td>0/4 (0%)</td>
<td>17/144 (11.8%)</td>
</tr>
<tr>
<td>HIV-1 RNA viral load &lt;50 copies/mL at delivery¹</td>
<td>78/81 (96.2%)</td>
<td>50/59 (84.7%)</td>
<td>3/5 (60%)</td>
<td>131/145 (90.3%)</td>
</tr>
<tr>
<td>HIV RNA viral load &lt;200 copies/mL at delivery¹</td>
<td>79/81 (97.5%)</td>
<td>54/59 (91.5%)</td>
<td>4/5 (80%)</td>
<td>137/145 (94.5%)</td>
</tr>
<tr>
<td><strong>Perinatal Outcomes</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Mean gestational age at delivery in weeks (range)</td>
<td>38.1 (26-40.5)</td>
<td>37.9 (30-41)</td>
<td>39.0 (38.2-40.3)</td>
<td>38.1 (26-41)</td>
</tr>
<tr>
<td>Mean birth weight in grams (range)</td>
<td>3126 (450-4560)</td>
<td>3176 (2863-3360)</td>
<td>2911 (990-4850)</td>
<td>3043 (450-4850)</td>
</tr>
</tbody>
</table>
Preterm birth (<37 weeks) | 16/83 (19.2%) | 10/59 (16.9%) | 0/5 (0%) | 26/147 (17.7%)  
Cesarean delivery for HIV | 0 | 5 | 1 | 6  

**Infant Outcomes**

| Fetal anomaly - Includes | 2/85 (2.4%) | 4/60 (6.7%) | 0/5 (0%) | 6/147 (4.1%)  
Anatomic/syndromic/genetic abnormalities |  
Perinatal HIV transmission | 0 (0%) | 1 (1.7%) | 0/5 (0%) | 1 (0.7%)  

1 Defined as viral load within 4 weeks of childbirth.
2 Anomalies include one infant with Tetralogy of Fallot and penis chordae, and one infant with mosaic 8p with an atrial septal defect and absence of corpus callosum.
3 Anomalies include one infant with a bicuspid aortic valve and ventricular septal defect, one infant with 14mB duplication resulting in hypotonia, one infant with heterotaxy syndrome, and one infant with a supernumerary digit.
4 n=57 as birthweight was missing for two infants.